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Catalytic, Asymmetric Mannich-Type Reactions of *N*-Acylimino Esters for Direct Formation of N-Acylated Amino Acid Derivatives. Efficient Synthesis of a Novel Inhibitor of Ceramide Trafficking, HPA-12

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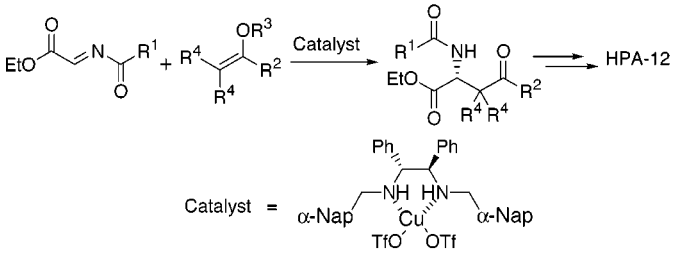
ABSTRACT



Catalytic, enantioselective Mannich-type reactions of *N*-acylimino esters for direct formation of N-acylated amino acid derivatives are described. A chiral copper catalyst prepared from Cu(OTf)$_2$ and a chiral diamine ligand is used. A novel inhibitor of ceramide trafficking, HPA-12, is efficiently synthesized using this reaction.

Many biologically important, chiral N-acylated amino acid derivatives are observed in Nature.[1] In particular, our laboratories have focused on (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12, **1**) (Figure 1), a new inhibitor of ceramide trafficking from endoplasmic reticulum to the site of sphingomyelin (SM) synthesis. HPA-12 is the first compound of a specific inhibitor for SM synthesis in mammalian cells and is expected as a drug that inhibits intracellular trafficking of sphingolipids.[2]

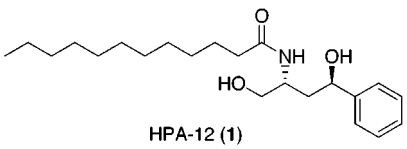


Figure 1. A novel inhibitor of ceramide trafficking, HPA-12.

For the synthesis of these compounds, catalytic enantioselective Mannich-type reactions[3] of α-imino esters with

(1) For example: (a) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298. (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Wälchli, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582. (c) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (d) von Döhren, H.; Keller, U.; Vater, J.; Zocher, R. *Chem. Rev.* **1997**, *97*, 2675. (e) Dickson, R. C. *Annu. Rev. Biochem.* **1998**, *67*, 27. (f) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532.

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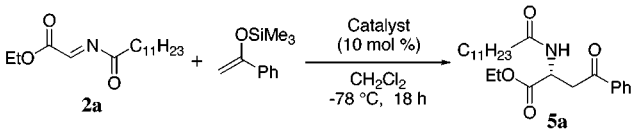
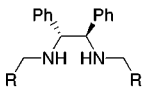
enolates would provide an efficient method. We have recently developed zirconium-catalyzed enantioselective Mannich-type reactions,[4] and other groups have also reported metal-catalyzed asymmetric Mannich-type reactions of α-imino esters.[5] In these reactions, however, the N-protected groups of the products have to be removed and then acylated.[6] More conveniently, *N*-acylimino esters would react with enolates to afford N-acylated amino acid derivatives directly. However, the starting materials, *N*-acylimino esters, are known to be unstable in several cases, and their use in organic synthesis has been limited. In this Letter, we report the first enantioselective Mannich-type reactions of *N*-acylimino esters using a chiral copper catalyst. Efficient synthesis of HPA-12 using this reaction is also described.

We have quite recently developed a convenient preparation method of *N*-acylimino esters using a polymer-supported amine.[7] According to this method, *N*-acylimino ester **2a** was prepared from the corresponding α-chloroglycine derivative,[8] and the Mannich-type reaction with the silyl enol ether derived from acetophenone was examined using a chiral catalyst. After screening various metals and chiral ligands, it was revealed that a chiral copper catalyst prepared from $Cu(OTf)_2$ and chiral ligand **3e**[9] was effective. The effects of chiral ligands and reaction conditions are summarized in Table 1. When $CuClO_4{\cdot}4CH_3CN$[10] was combined with (*S*)-xylyl-BINAP[11−13] and used as a catalyst, a low enantiomeric excess (ee) was obtained. On the other hand, in the presence of $Cu(OTf)_2$ and ligand **3e** (10 mol %), **2a** and the silyl enol ether were added successively to afford the desired adduct in 80% ee, but in low yield. In this case, formation of a dimer of **2a** was observed, presumably due to contamination by water. We carefully performed the reaction under anhydrous conditions, and the silyl enol ether was added to the catalyst first and then **2a** was slowly charged over 20 min.[14] The yield was dramatically improved, and the desired adduct was obtained in 92% yield with 94% ee.

Table 1. Effect of Chiral Ligands and Reaction Conditions



catalyst	yield (%)	ee (%)
$CuClO_4{\cdot}4CH_3CN$ + xylyl-BINAP[a]	69	12
$CuClO_4{\cdot}4CH_3CN$ + **3a**	62	8
$Cu(OTf)_2$ + **3a**	25	63
$Cu(OTf)_2$ + **3b**	32	63
$Cu(OTf)_2$ + **3c**	24	75
$Cu(OTf)_2$ + **3d**	12	52
$Cu(OTf)_2$ + **3e**	20	80
$Cu(OTf)_2$ + **3f**	32	64
$Cu(OTf)_2$ + **3e**	92	94[b]



3a: R = Ph **3d**: R = 3,5-di^{t}BuPh
3b: R = 4-MePh **3e**: R = 1-Nap
3c: R = 3,5-diMePh **3f**: R = 2-Nap

[a] (*S*)-(−)-Bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl. [b] 0 °C.

Several examples of the Mannich-type reactions are shown in Table 2. *N*-Acetylimino ester **2b** also reacted smoothly to afford the desired adduct in high yield with excellent ee. For *N*-benzoylimino ester **2c**, the use of $Cu(OTf)_2$-ligand **3e** only gave a low ee (58% yield, 14% ee). In this substrate, high ee's were obtained when $CuClO_4{\cdot}4CH_3CN$−(*S*)-xylyl-BINAP was used as the catalyst (Table 2, entries 6−9). As for enolate components, silyl enol ethers derived from ketones, an ester, and a thioester worked well. Moreover, it is noted that an alkyl vinyl ether also reacted smoothly to afford the corresponding N-acylated amino acid derivatives in high yields with excellent ee's. In the reaction of the alkyl

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(10) For the preparation of $CuClO_4{\cdot}4CH_3CN$, see: Kubas, G. J. *Inorganic Synthesis*; Shriver, D. F., Ed.; Plenum: New York, 1979; Vol. XIX, p 90.

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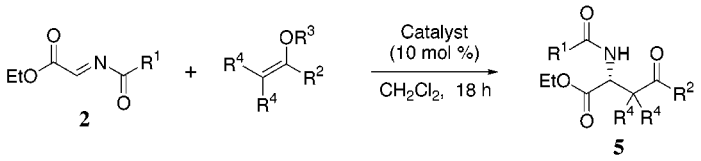
(14) Experimental details are shown in Supporting Information.

Table 2. Catalytic Asymmetric Mannich-Type Reactions



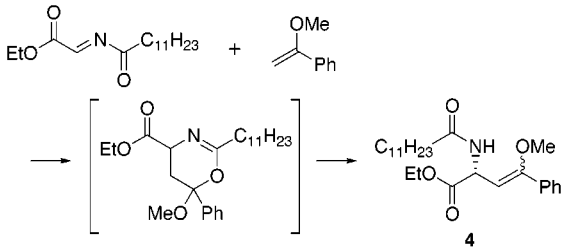
2 **5**

no.	R^1	R^2	R^3	R^4	cat.[a]	temp (°C)	product	yield (%)	ee (%)[b]
1	$C_{11}H_{23}$ (**2a**)	Ph	$SiMe_3$	H	A	0	**5a**	92	94
2	$C_{11}H_{23}$ (**2a**)	MeOPh	$SiMe_3$	H	A	0	**5b**	97	92
3	$C_{11}H_{23}$ (**2a**)	ClPh	$SiMe_3$	H	A	0	**5c**	88	93
4	$C_{11}H_{23}$ (**2a**)	Ph	Me	H	A	0	**5a**	85	90
5	CH_3 (**2b**)	Ph	$SiMe_3$	H	A	0	**5d**	85	94
6	Ph (**2c**)	Ph	$SiMe_3$	H	B	−78	**5e**	79	97
7	Ph (**2c**)	MeO	$SiMe_3$	Me	B	−78	**5f**	81	96
8	Ph (**2c**)	EtS	$SiMe_3$	H	B	−78	**5g**	76	90
9	Ph (**2c**)	Ph	Me	H	B	−78	**5e**	77	95

[a] A: $Cu(OTf)_2$ + **3e**. B: $CuClO_4 \cdot 4CH_3CN$ + (*S*)-xylyl-BINAP. [b] For determination of absolute configurations, see Supporting Information.

vinyl ether, the initial adduct was vinyl ether **4**, which was converted to the corresponding amino acid derivative **5** under acidic conditions. A possible mechanism for the formation of **4** is [4 + 2]-cycloaddition of **2a** and the alkyl vinyl ether followed by proton transfer (Scheme 1).[15] In the reactions

Scheme 1



4

of silyl enol ethers, similar intermediates that were less stable than **4** were observed in the reaction pots. In this mechanism, it is noteworthy that chiral induction by the chiral catalyst occurred at the initial [4 + 2]-cycloaddition stage.

Finally, synthesis of HPA-12 was performed using the present asymmetric Mannich-type reaction. We have quite recently performed the first asymmetric synthesis of HPA-12 using a chiral zirconium-catalyzed enantioselective Mannich reaction as a key step.[16] In this synthesis, however, the N-protected group of the product was removed and then acylated for the preparation of the N-acylated amino acid derivative, and total efficiency was moderate (total yield 6.0%, six steps). The Mannich-type adduct (**5a**) was treated with K-Selectride at −78 °C for 2 h[17] and then $LiBEt_3H$ at rt for further 2 h (one-pot) to afford HPA-12 in high yield (Scheme 2). It should be noted that HPA-12 has been

Scheme 2

5a **1**

synthesized from **2a** in three steps (two-pot) and that the total yield was 68.6%. According to this efficient synthetic pathway, the preparation of many other HPA-12 analogues is feasible.

In summary, the first asymmetric Mannich-type reactions of *N*-acylimino esters with enolates have been achieved using a novel chiral copper catalyst.[18] As enolate components, silyl enol ethers as well as a vinyl ether reacted smoothly. This is the first example of using a vinyl ether in catalytic asymmetric Mannich-type reactions.[19] Moreover, a new type of reaction mechanism of the catalytic asymmetric Mannich-type reactions has been proposed. Catalytic enantioselective synthesis of a novel inhibitor of ceramide trafficking, HPA-12, has been attained in three steps (two-pot) using this novel asymmetric reaction.

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Supporting Information Available: Experimental details and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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